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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,065	05/31/2002	Gayle Delmonte Wetzel	MSB-7265-PCT-US	1911

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,065	WETZEL, GAYLE DELMONTE	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *7-9,11,13 and 15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,10,12 and 14* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II drawn to methods of inhibiting angiogenesis by administering a BTL.012-like protein of Claims 1-6, 10, 12, and 14 in the reply filed on 10/29/04 is acknowledged.

Status of the Claims

Claims 1-21 are pending. Claims 7-9, 11, 13, and 15-21 are withdrawn as being drawn to non-elected subject matter. Claims 1-6, 10, 12, and 14 have been considered in this Office Action.

Examiner's note concerning References Cited

WO 99/37660 has been cited in the present Office Action. Given that WO 99/37660 was cited in the international application from which this application is derived, given that the reference was provided by Applicants upon filing the present application, and given the volume of the WO 99/37660 reference (600 pages), the reference has been cited but not provided with this Office Action.

Objections to the Specification

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. The present application claims priority to provisional application no. 60/266,300.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/16716 (the '716 publication).

The term "BTL.012-like protein" recited in the claims has been interpreted to include any thrombospondin repeat protein. The '716 publication teaches a method of inhibiting angiogenesis by administering fragments of a thrombospondin repeat protein (p. 8). The '716 publication also teaches a method of modulating the formation of human endothelial cels into capillary-like structures comprising contacting the cells with

a biologically effective amount of a composition comprising a thrombospondin repeat protein ("BTL.012-like protein") (p. 33-35).

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Nishimori et al. (Oncogene (1997) 15: 2145-2150).

The term "BTL.012-like protein" recited in the claims has been interpreted to include any thrombospondin repeat protein. Nishimori et al. teach a method of inhibiting angiogenesis by administering the "BTL.012-like protein" (a protein with thrombospondin repeats) BAI1 (see abstract). Nishimori et al. teach that when rat corneas were contacted with BAI1, their ability to recruit new blood vessels was inhibited (p. 21, Col. 1). Since formation of cells into capillary-like structures is part of the angiogenesis process, it would be inherent that the method described by Nishimori et al. would have caused inhibition in the formation of cells into capillary-like structures.

Claims 1, 5, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/37660 ("the '660 publication").

The term "BTL.012-like protein" recited in the claims has been interpreted to include any thrombospondin repeat protein. The '660 publication teaches a method of inhibiting angiogenesis by administering METH1 or METH2 (a "BTL.012-like protein" with thrombospondin repeats) (p. 123, Ex. 4). The '660 publication also teaches a method of modulating the formation of human endothelial cells into capillary-like structures comprising contacting the cells with a biologically effective amount of a composition comprising METH1 or METH2 (p. 127, lines 11-23).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 10, 12, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods of inhibiting angiogenesis by administering a "BTL.012-like protein" or a protein with an amino acid sequence which is at least 60% identical over at least 40 residues or at least 70% identical over at least 30 residues to SEQ ID NO:1. Thus, the scope of the claims includes using innumerable structural variants and the genus is highly variant because a significant number of structural differences between genus members is permitted. Moreover, the present Specification does not provide any guidance as to what changes could be made without losing angiogenesis inhibiting activity. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. In other words, those of skill

in the art could not recognize which proteins in the claimed genus would be successful in inhibiting angiogenesis. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus of proteins that could be used to inhibit angiogenesis.

Claims 1, 3-6, 10, 12, and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting angiogenesis comprising administering an effective amount of a protein having the sequence of SEQ ID NO:1 or a method of modulating the formation of cells into capillary-like structures comprising contacting the cells with a biologically effective amount of a composition comprising a protein having the sequence of SEQ ID NO:1 does not reasonably provide enablement for methods of inhibiting angiogenesis, inhibiting formation of cells into capillary-like structures, or methods of treatment using any "BTL-like protein" or any protein having at least 60% identity over 40 residues of SEQ ID NO:1 or at least 70% identity over 30 residues of SEQ ID NO:1, or a method of treating or preventing medical conditions of the claims using the claimed proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.
Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.

1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the Claims:

The claims are so broad as to include methods of inhibiting angiogenesis or treating a disease by administering proteins of almost any sequence ("BTL.012-like" is defined as a protein sequence with at least 60% identity to at least 20 amino acid residues of SEQ ID NO:1; see p. 9, middle paragraph of Specification). The claims also include methods of preventing any medical condition or methods of preventing any cancer, metastasis, diabetic retinopathy, macular degeneration, cardiovascular diseases, and wounds.

Nature of the Invention:

The nature of the invention involves the discovery in a cDNA library of a thrombospondin repeat protein that was found to inhibit HUVEC and MLuEC capillary-like organization in an in vitro assay (p. 26 of present specification). Given the lack of knowledge of how thrombospondin repeat proteins inhibit angiogenesis and given the number of proteins involved in angiogenesis, the nature of the invention is complex. Given that the term cancer encompasses diseases of many different tissues caused by completely different mechanisms, the nature of preventing or treating cancer is complex.

Amount of direction or guidance presented and Working Examples:

The present Specification provides an example of using a FLAG-BTL012 (BTL012 = SEQ ID NO:1) fusion protein in in vitro methods of inhibiting HUVEC and MLuEC capillary-like organization. The present specification does not describe what part of the amino acid sequence of SEQ ID NO:1 is essential for the inhibitory activity or what other proteins within the scope of the claims might have anti-angiogenic activity. The present Specification only generally states that the diseases of the claimed invention can be treated by administering a BTL.012-like protein but does not provide any specifics such as what types of cancers or cardiovascular diseases could be treated or how much of the protein should be administered for an effective treatment.

The state of the prior art and relative skill of those in the art:

The state of the prior art is such that proteins that are considered "BTL.012-like" were known to inhibit angiogenesis. However, the discovery that these protein have anti-angiogenic activity was based on knowledge of their function. For example, with knowledge of the role of p53 in angiogenesis, Nishimori et al. examined the anti-angiogenic activity of BAI1 because, as a p53-target gene, it was a strong candidate of the angiogenesis that accompanies progression of glia-derived tumors. The '716 publication, described above, with knowledge of the role of thrombospondin as an angiogenesis inhibitor, discloses a random search of peptides within the thrombospondin sequence that would inhibit angiogenesis. However, neither Nishimori et al. nor the '716 publication teach the mechanism of angiogenesis inhibition or what characteristics of the sequence would allow for the inhibition. In fact, Nishimori et al.

indicate that it is unclear why one out of three TSP-type-1 repeats failed to suppress angiogenesis (p. 2149, Col. 1, 1st paragraph).

The state of the art is such that methods of preventing cancer, metastasis, diabetic retinopathy, macular degeneration, and some cardiovascular diseases, while thoroughly studied, have not been realized. For example, Constable (MJA (2004) 181(9): 471-472) teaches that definitive treatment does not yet exist for macular degeneration and Sjolie et al. (Diabet. Medicine (2004) 21: 666-672) teaches that treating diabetic eye complications and preventing visual loss in people with diabetes is still a challenge.

Predictability or unpredictability of the art:

Given that the mechanism of inhibition of angiogenesis by the thrombospondin repeat proteins is unknown as evidenced by the prior art described above and that those of skill in the art do not know what specific sequences are essential for angiogenesis inhibition, choosing the amino acid sequences that would be successful in inhibiting angiogenesis would be highly unpredictable.

In addition, given that the mechanism of pathogenesis of many cancers, macular degeneration, diabetic retinopathy, many cardiovascular diseases is not well understood, preventing or treating these diseases with a protein that has been characterized only in that it is anti-angiogenic in vitro, is highly unpredictable.

Quantity of experimentation:

Given the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the limited number of working examples only relating to SEQ ID NO:1, the complex nature of the invention, the state of the prior art which establishes that the mechanism of inhibition is unknown and the sequences that are essential to inhibition are unknown, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the disclosed BTL.012 protein that are required for the functional and structural integrity of the protein. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Claim Objections

Claims 1-4, 12, and 14 are objected to for reciting non-elected subject matter. Claims 1-4, 12, and 14 are drawn to methods of "modulating" angiogenesis by methods other than administering the BTL.012 protein (by gene therapy for example). Correction is required.

Claims 10 and 12 are objected to for depending from non-elected claims 9 and 7, respectively. Correction is required.

Claim 2 is objected to because it depends from a rejected claim. However, claim 2 would be allowable if rewritten in independent form to include all of the limitations of Claim 1.

Conclusions

No Claims are allowable. Claims 1, 3-6, 10, 12, and 14 are rejected. Claim 2 is objected to. However, a method of inhibiting angiogenesis comprising administering a composition comprising a protein having the sequence of SEQ ID NO:1 and a method of inhibiting the formation of endothelial cells into capillary-like structures comprising contacting the cells with a biologically effective amount of a composition comprising the protein of SEQ ID NO:1 appears to be free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
November 23, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER